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Characterization of detrended fluctuation analysis in the context of glycemic time series

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***Abstract*— There is a growing interest in the analysis of hyperglycemia and its relationship with other pathologies. The level of glucose in blood is regulated by the flux/reflux and controlled by hyperglycemia hormones and hypoglycemic insulin. Glycemic profiles are characterized by a nonlinear and nonstationary behavior but also influenced by circadian rhythms and patient daily routine which introduce quasi–periodic trends into them.**

This type of signals are commonly analyzed by Detrended Fluctuation Analysis (DFA) which states that the control system in charge of regulating the glucose level usually holds a long–range negative correlation. But there is an inconsistency about the windowing lengths, as no standard or rules are set.

This work studies the influence of the windowing length sequence, and shows that there is a need for selecting the optimal values in order to obtain a good differentiation between different groups, and these values are somehow determined by signal characteristics.

I. INTRODUCTION

In the last years, there has been a great interest in the analysis of hyperglycemia and its relevance or association with other cardiovascular pathologies or illnesses. The level of glucose in blood is regulated by the flux (ingestion and/or breakdown) and the reflux (uptake and/or storage), and controlled by hyperglycemia hormones and hypoglycemic insulin. This physiological control system usually holds a long–range negative correlation [1].

Physiological systems are thought to be regulated by complex and nonlinear processes. These systems not only exhibit a stationary or periodical behavior, but they also show a nonpredictable, chaotic, nonlinear and nonstationary one [2]. Recently, nonlinear methods, such as entropy estimations or data complexity statistics, have been applied to the analysis of biological signals, as they provide better and more reliable results for these type of systems, where traditional linear methods lack of robustness or characterization depth as they implicitly assume the stationarity of the signal [3], [4].

Most of the studies on hyperglycemia use the regularity estimator metric known as Detrended Fluctuation Analysis (DFA). These studies are aimed at characterizing the power–law correlations existing in glycemic time series. DFA is a signal regularity measure that estimates the entropy of a time series by allowing the detection of long–range correlations embedded in an apparently nonstationary data series. As it only considers the fluctuations from local trends, DFA has the ability to avoid the spurious detection of presumed long–range correlations that are artifacts of nonstationarity or introduced by external trends. On the other hand, DFA is quite sensitive to the data–set length N. If the time series is short, DFA may exhibit large fluctuations [5], [6].

DFA consists in estimating a modified root mean square of a random walk over a set of signal lengths. Different authors define a number of ways for segmenting the signals in order to carry out their analysis. However, there is not an unanimous way of doing it. For example, [5] sets the maximum value to the length of the signal (N), whereas [7] establishes it on N/4 and [8] on N/10.

The results obtained by DFA are indicated by the value of an output parameter known as the scaling exponent α. Large values of α denote smoother and more predictable time–series. Different authors establish a number of intervals for power–law correlations in terms of α. For example, in [5], 3 intervals were defined. The first one (0,0.5) accounts for different type of power–law correlations, the second one (0.5,1] denotes persistent long–range power-law correlations in the signal and finally, if $\alpha > 1$, it entails that correlations exist but cease to be of a power–law form. Other works such as [7], set a boundary for α in 0.5. If α is below 0.5, data are anti–correlated, whereas if α is greater than 0.5, the signal can be considered long–range correlated. In the context of glycemic time series, an indication of hyperglycemia in patients could be the segmentation proposed in [9], where if α is greater than 1.5, a positive correlation exists, otherwise, a negative correlation is considered.

This paper aims to characterize the influence of the DFA windowing sequence, illustrated by means of a segmentation study of glycemic time series from healthy controls (HC), metabolic syndrome (MS) patients (considered as a prediabetic condition) and type 2 diabetes mellitus (DM) patients

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from the internal medicine unit of a university hospital. The objective of the work was to propose a robust scheme for setting an optimal windowing sequence that provides the best separation among signal classes. The experimental set was obtained at the Intern Medicine Unit of the University Hospital of Mostoles, Madrid (Spain) [10].

II. METHOD

The method proposed is based on the DFA metric. This measure has provided good results in previous glycemic series studies [1], [9], [10], where more common similar metrics such as Approximate Entropy (ApEn) or Sample Entropy (SampEn) failed to discern among record types, despite parameterization studies.

DFA is computed for a series of window lengths, and then a statistical analysis is carried out to find the optimal length value for signal segmentation. These method steps are described next.

A. DFA computation

DFA is computed as a modified root mean square of a random walk. The DFA algorithm is as follows:

Given an input time–series $u(n)$ with $n = 0, 1, \ldots, N-1$ (with $N = 288$ in this case), the first step is to generate the random walk [6] by integrating $u(n)$:

$$U(k) = \sum_{i=0}^{k} u(i) - \bar{u}, \text{with } k = 0, 1, \ldots, N-1 \qquad (1)$$

where $\bar{u}$ denotes the mean value of the complete time–series $u(n)$. Some researchers consider that if records are not long enough, this integration could be omitted [11]. However, we chose to include this step to follow the standard DFA algorithm.

The resulting integrated sequence $U(k)$ is then windowed according to a length parameter L_i. The specific values of L will be studied and defined in Sec. II-B. This parameter represents the length of non–overlapping rectangular time windows. We will refer as M the maximum number of windows of length L_i that can be allocated in the time series of length N.

Inside each window $W_j, j = 1, \ldots, M$ of length L_i, a least–square line is fitted to the data. Then, using these approximation lines, an estimate of the local trend at each point k, denoted as $U_{W_j}(k)$, is computed. This local trend is removed from the data, $U(k) - U_{W_j}(k)$, with $k \in W_j$, and the mean square fluctuation F_L of the integrated and detrended time series can then be computed for a specific window length, according to [5]:

$$F_L = \sqrt{\frac{1}{N} \sum_{k=0}^{N-1} \left(U(k) - U_{W_j}(k)\right)^2} \qquad (2)$$

The calculation of F_L is repeated for a number of different lengths L_i up to a maximum one. The result of the algorithm, the scaling exponent α, is obtained as the slope of the line relating the log–log plot of F_L against L_i, [5], $F_{L_i} \propto L_i^{\alpha}$. This process is graphically illustrated in Fig.1.

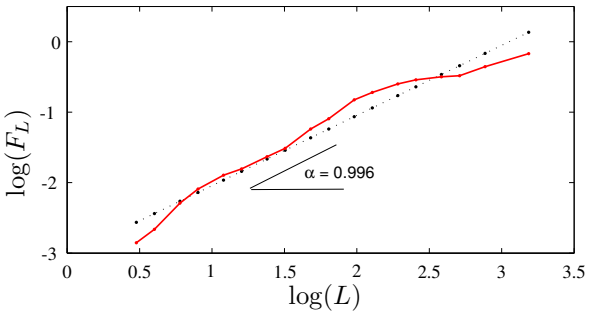

Fig. 1. Graphical example of the process involved in the computation of α. Horizontal axis corresponds to the log scale of length values. Vertical axis corresponds to log values calculated for fluctuation F for different lengths. Dotted line represents the least squares fitted line.

Other researchers, like [6], [7], [12] propose the computation of an instantaneous DFA coefficient and even others recommend the use of 2 scaling exponents as in [7], [9], one for short–range and the other for long–range correlations. We again chose to follow the standard DFA scheme.

B. Window Length Sequence

The scaling exponent greatly depends on the proper selection of the windowing sequence $L = \{L_1, L_2, \ldots, L_n\}$.

In this work, we decided to consider different windowing sequences that spanned up to the complete signal length, for characterization purposes. Two type of sets were considered, in the first type all the windowing sequences had an initial value equal to the DFA order plus 2 [5], $L_1 = 3$, being DFA order the order of the polynomial used in the detrending step. In the second set type all windowing sequences had the same last value equal to the signal length, this is, $L_n = 288$.

Each windowing length consider had to satisfy $L_i \ni \text{mod}(N, L_i) = 0$, so no samples were discarded. The possible windowing lengths to be considered were $L_i = \{3, 4, 6, 8, 9, 12, 16, 18, 24, 32, 36, 48, 72, 96, 144, 288\}$.

C. Statistical analysis

The resulting α values were screened with the Shapiro–Wilk normality test. This test is recommended when the number of observations is low, as this was the case. The null hypothesis states that data come from a normal distribution. If pValue is lower than 0.05, the null hypothesis can be rejected. If data were assumed to come from a normal distribution, a further Student T-test was performed so as to provide an statistical value to be used as the input for a signal qualitative segmentation process (DM vs. CH vs. MS). The lower the probability, the larger the difference between mean values of each distribution, which implies that a better segmentation could be obtained. If data could not be considered to be generated by a normal distribution, the Mann–Whitney U significance test was used in order to compare median values instead.

The confidence intervals for the α results were estimated as:

$$CI = [\mu - 2\sigma_\mu, \mu + 2\sigma_\mu] \tag{3}$$

where μ corresponds to the mean and σ_μ to the Standardized Mean Error (SME), in case values were assumed to come from a normal distribution. The SME is computed as:

$$\sigma_\mu = \frac{\sqrt{\left(\frac{\sum_{i=1}^{n}(\alpha_i - \mu)^2}{n}\right)}}{\sqrt{n}} = \frac{\sigma}{\sqrt{n}} \tag{4}$$

Otherwise, μ and σ_μ correspond to the median and median absolute deviation (MAD), respectively, where MAD is obtained then as:

$$\sigma_\mu = \underset{n}{\text{median}} \{|\alpha(n) - \text{median}\{\alpha(n)\}|\} \tag{5}$$

The variable n accounts for the total number of values on each data group.

III. EXPERIMENTAL DATASET

The glycemic profile database used in this work considers 10 patients with MS, 10 patients with type 2 DM and 10 control subjects. All of them were selected from the outpatient internal medicine and vascular risk clinics at the Móstoles University Hospital. DM patients were selected according to a fasting glucose level larger than 126 mg/dl (confirmed in a second measurement) and MS patients were selected according to the NCEP–ATPIII criteria [13].

A glycemic value sample was acquired every 5 minutes, during a time period of 24 hours. The signal lengths were limited to a total of 288 samples.

A deeper characterization of each group considered for the analysis can be found in [10].

IV. RESULTS

Segmentation results between DM, HC and MS groups are shown in Fig.2 for each of the different L considered. Fig.2.a show the results for the increasing L in terms of the last windowing length L_n considered for the detrending step of DFA, for a sequence starting in L_1=3 while Fig.2.b shows them in terms of the initial windowing length in the sequence when the maximum length is fixed at L_n = 288.

It can be appreciated that for shorter sequences (initial ones in Fig.2.a and last ones in Fig.2.b) the variability of the scaling exponent α is larger than for the larger ones. For increasing L (Fig.2.a) DM has always larger value than HC or MS, this implies softer time–series, less variability and larger regularity. For decreasing windowing sequences (Fig.2.b) DM presents a lower value for shorter windowing sequences which increases when increasing the number of windows in the sequence.

When an increasing windowing sequence L is considered, segmentation between the three groups simultaneously only occurs when $L_i \geq 72$ samples (6h), Table I shows statistical probability for Student T-Test as data could be assumed to come from a normal distribution ($p \geq 0.3$), segmentation between DM and HC occurs for any windowing sequence with $L_n \geq 12$ (1h) with $p \leq 0.020$.

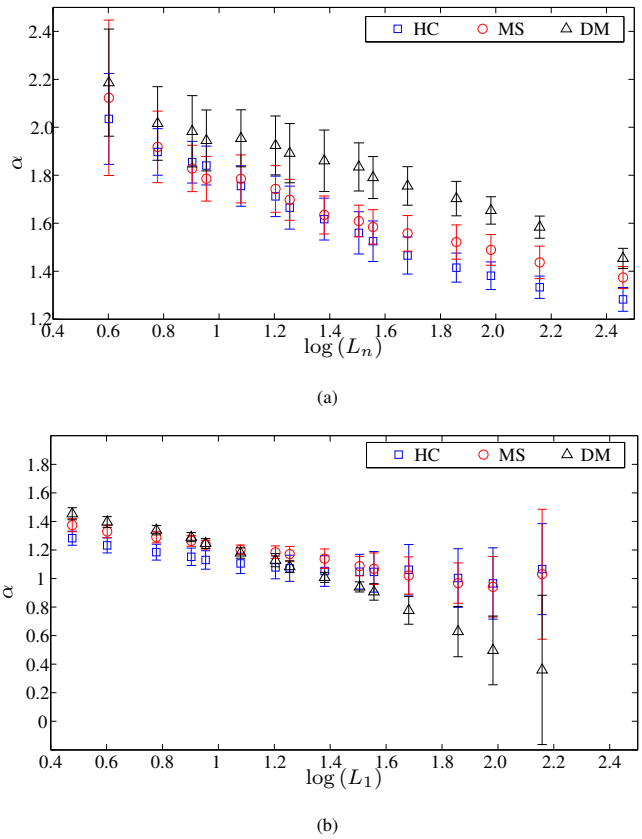

Fig. 2. Scaling exponent α confidence intervals for different lengths considered for the (a) last windowing length in sequence and (b) initial windowing length in the sequence for the three classes: healthy controls (HC, blue squares), patients with metabolic syndrome (MS, red circle) and type 2 diabetes mellitus patients (DM, black triangle)

If a decreasing windowing sequence L is preferred, segmentation only takes place between the three groups simultaneously if $L_1 = 3$ (results are shown in Table I.(d)). Separation between DM and HC occurs for windowing sequences with $L_1 = \{4, 6, 8, 9, 72, 96, 144\}$ ($p \leq 0.047$).

V. DISCUSSION

As expected, windowing sequences considering a larger number of lengths provide scaling factors with less variability (narrower confidence intervals). Lower α are generally associated with HC rather than with DM patients if increasing widowing sequences are chosen (Fig.2.a) just as in [1] or as in [9], not being the case when decreasing windowing length are considered, as HC show larger α values for larger windowing sequences than for shorter ones.

This phenomenon needs to be looked at carefully, as for increasing L with $L_n < 12$ which is approximately 1h duration, no segmentation is obtained, this tells us that the system in charge for glycemic regulation is not yet

TABLE I

STATISTICAL RESULTS FOR INCREASING L, SHOWN ONLY FOR THOSE WHERE SEGMENTATION BETWEEN THE THREE GROUPS OCCUR. (A) $L_n = 72$, (B) $L_n = 96$, (C) $L_n = 144$ AND (D) $L_n = 288$

	MS	DM
HC	0.041	0.000
MS		0.005

(a)

	MS	DM
HC	0.028	0.000
MS		0.004

(b)

	MS	DM
HC	0.018	0.000
MS		0.008

(c)

	MS	DM
HC	0.023	0.001
MS		0.034

(d)

activated (Fig.2.a). Then segmentation is clearer in mid–term windowing sequences ($1.8 < log_{10}(L_n) < 2.2$) where not only DM are isolated from HC but both are also differentiated from MS. When considering the last windowing length ($L_n = 288$), segmentation is obtained but p increased, this can be due to residual effects or influences in the glucose–regulation system which are out of our boundaries. This is even more evident when considering decreasing windowing length (Fig.2.b) as if $log_{10}(L_1) > 1.2$ DM patients show lower scaling exponent, which tell us that DM signals are less regular or predictable (more complex) what is not physiologically justifiable and against all actual literature.

Finally from what has been studied in this paper we can infer that the effects of the glucose regulation system has more to do with mid–term or long–term effects rather than with short–time effects.

VI. CONCLUSION

In this paper, a detailed characterization analysis of the windowing sequence length influence on DFA segmentation of glycemic profile records has been presented. Analyzing glucose levels in blood is a key factor for glucose metabolism disturbance detection and it can be related to other major cardiovascular illnesses and death.

On previous studies, only segmentation between DM and HC [9], [10] or between SV and NSV [1] classes was reported. Other authors defined and used different maximum windowing sequence lengths with no clear rationale. In our study, we have illustrated the fact that by choosing the appropriate sequence length, segmentation can be obtained not only between DM and HC classes, but also between DM and MS or MS and HC patients, which could allow experts clinicians to do an earlier prognosis and treatment.

Choosing and adequate windowing sequence is crucial to obtain good segmentation results. Depending on the kind of effects that the method should address, short–term, mid–term or long–term effects, different windowing sequences with larger maximum lengths should be chosen so as to obtain reliable and robust results.

If the windowing sequence was obtained in an arbitrary way, the expected results could be masked by DFA properties, and result in no class segmentation obtained, even when there is an underlying segmentation that an adequate windowing sequence could have unveiled.

As current and further work, a deeper study concerning windowing sequences lengths is presently being done, using different biosignal databases and types. The consideration of more than one scaling exponent is being also studied as proposed in [7], [14] with an automatic data dependent threshold selection to establish where the boundary between each different scaling exponent is located. Finally, the evolution of an adaptive instantaneous scaling exponent is being evaluated over several types of signals.

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